PROGESTERONE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a National Stage application under 35 U.S.C. § 371 of International Application Ser. No. PCT/US2013/046442, entitled "PROGESTERONE FORMULATIONS" which was filed on Jun. 18, 2013, and claims priority to the following U.S. Patent Applications: U.S. Provisional Application Ser. No. 61/661,302, entitled "ESTRADIOL FORMULATIONS," which was filed on Jun. 18, 2012; U.S. Provisional Application Ser. No. 61/662,265, entitled "PROGESTERONE FORMULATIONS," which was filed on Jun. 20, 2012; U.S. patent application Ser. No. 13/684,002, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Nov. 21, 2012; U.S. Patent Application Ser. No. PCT/US2013/023309, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Jan. 25, 2013; U.S. patent application Ser. No. 13/843,362, entitled "TRANSDERMAL HORMONE REPLACEMENT THERAPIES," which was filed Mar. 15, 2013; and U.S. patent application Ser. No. 13/843,428, entitled "NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES," which was filed Mar. 15, 2013. All aforementioned applications are hereby incorporated by reference herein in their entirety.

FIELD OF INVENTION

The disclosure relates to progesterone formulations. Various progesterone formulations may be used in hormone therapies for menopausal, peri-menopausal and post-menopausal females, for example, to mitigate side effects from estrogen replacement therapy. In addition, various progesterone formulations may be used to prevent preterm delivery in pregnant women having a shortened cervix.

BACKGROUND OF THE INVENTION

Hormone replacement therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to supplement hormone levels in women who lack adequate hormone production. It can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones.

HRT is available in various forms. One therapy involves administration of low dosages of one or more estrogen(s) or one or more chemical analogues. Another involves administration of progesterone or one or more chemical analogues. Among other effects, progesterone administration acts to mitigate certain undesirable side effects from estradiol administration or naturally-occurring elevated blood levels including endometrial hyperplasia (thickening) and prevention or inhibition of endometrial cancer. Progesterone is a C-21 steroidal sex hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone is hydrophobic, having a reported aqueous solubility of 0.007±0.0 mg/ml. Progesterone is poorly absorbed when administered orally.

Conventional progesterone therapeutics include the administration of PROMETRIUM (progesterone, USP) (Abbott Laboratories, Chicago, Ill.). PROMETRIUM is an FDA-approved drug, formulated in a peanut oil-based medium, containing micronized progesterone, but with a relatively large particle size fraction.

The active ingredient is considered to be structurally identical to naturally occurring progesterone produced by a woman's body (also known as a "bioidentical).

Clinical trials involving PROMETRIUM have shown significant patient variability. For example, a clinical trial involving postmenopausal women who were administered PROMETRIUM once a day for five days resulted in the mean pharmacokinetic parameters listed in Table 1 (see Table 1, package insert for PROMETRIUM).

TABLE 1

Pharmacokinetic Parameters of PROMETRIUM Capsules

	PROMETRIUM Capsules Daily Dose		
Parameter	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 ± 21.9	38.1 ± 37.8	60.6 ± 72.5
T_{max} (hr)	1.5 ± 0.8	2.3 ± 1.4	1.7 ± 0.6
AUC (0-10)(ngxhr/ml)	43.3 ± 30.8	101.2 ± 66.0	175.7 ± 170.3

The unusually high variability in the Cmax and AUC, as evidenced by the large reported standard deviation, indicates that a significant percentage of patients are overdosed or receive a sub-optimal dose.

The presence of peanut oil in the formulation excludes patients who are allergic to peanut oil. Peanut oil, like other peanut products, may act as an allergen. Indeed, there is a portion of the population that has severe reactions to peanut oil. Peanut allergies are becoming a significant health concern. Food allergies are a leading cause of anaphylaxis, with approximately 200 deaths occurring annually in the United States. While incidence and prevalence are not entirely known, it is suspected that about 6% of children and 4% of adults in North America are affected by food allergies. Many food allergies experienced by children are generally outgrown in adulthood with the exception of peanut allergies.

Progesterone and its analogues can be used to treat a variety of medical conditions, including acute diseases or disorders, as well as chronic diseases and disorders associated with long-term declines of natural progesterone levels.

Accordingly, improved formulations of progesterone would be advantageous.

SUMMARY OF THE INVENTION

Various pharmaceutical formulations are disclosed herein. For example, pharmaceutical formulations are disclosed comprising ultra-micronized progesterone. Moreover, pharmaceutical formulations are disclosed comprising formulations of ultra-micronized progesterone, wherein the ultra-micronized progesterone is combined with a suitable excipient.

Thus, in various illustrative embodiments, the invention comprises an encapsulated liquid pharmaceutical formulation for orally administering progesterone to a mammal in need thereof, said formulation comprising: progesterone, as the sole active pharmaceutical ingredient, in micronized form, in solubilized form, or in micronized and partially soluble form in a carrier that comprises a medium chain fatty